2. Support for amendments to the claims

Support for the amendments to the claims can be found throughout the specification, the drawings, and the claims as originally drafted. Support for new claims 24 and 25 can be found on, e.g., page 8, lines 26-28 of the present application. No new matter is introduced.

3. Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1-3, 5, 6, and 8-23 under 35 U.S.C. § 112, second paragraph because the term "disease" is allegedly indefinite. According to the Examiner, the specification does not define a scope of conditions that are encompassed by the term and therefore any condition that is a deviation from a reference condition can be considered a disease. To the extent the Examiner believes that the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

As amended, the claim recites "a disease associated with chromosomal rearrangement." Thus, the claims are directed to methods involving comparison of reference genome sequences to sequences from a genome from an individual with a disease associated with chromosomal rearrangement. Thus, the terms used in the claims are clear to those of skill in the art.

Applicants note that the scope of a claim term is not a basis for rejecting the term as indefinite. *See* MPEP 2173.03 entitled "Breadth is not Indefiniteness." The Examiner does not appear to be confused about what the term "disease" means. Indeed, it is a common term in the English language. Instead, the Examiner's rejection is apparently raised because "disease" can encompass any condition. Thus, to the extent the rejection is based on a rejection of the claim's scope, the rejection is improper.

In light of the above discussion, Applicant's respectfully request withdrawal of the rejection.

3. Rejection under 35 U.S.C. § 102

Claims 1, 3, and 11 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Brosch *et al.* According to the Examiner, the reference describes determining terminal sequences of BAC clones. In addition, the Examiner argues that the reference describes comparing the clones to total genomic DNA from *M. tuberculosis* and identifying the differences. With regard to the phrase "individual with disease" in claim 1, the Examiner states that "the library in the reference is obtained from tuberculosis bacterium." *See*, Final Office Action, page 3. Applicants respectfully traverse the rejection.

As noted in previous responses, a reference may anticipate a claim under 35 U.S.C. §102(b) only if the reference contains each and every element of the claimed invention. Brosch *et al.* clearly does not describe several different elements of claim 1.

First, Brosch *et al.* does not teach or suggest analysis of a genome from an individual with disease associated with chromosomal rearrangement. To the extent the Examiner addresses this issue, the Examiner states that the library described in Brosch *et al.* is from a tuberculosis bacterium. While the bacteria may very well be capable of causing disease *in* humans, the bacteria *itself* is not diseased. In addition, there is no reference to the bacteria having a disease associated with chromosomal rearrangements.

Second, Brosch *et al.* does not describe performing the following steps of claim 1:

(ii) obtaining sequence information from the termini of each of said plurality of clones, thereby obtaining a pair of terminal sequences;

(iii) identifying a pair of sequences within said reference genome that corresponds to each of said pairs of terminal sequences; and

(iv) determining the relationship between the members of each pair of corresponding sequences within said reference genome.

While Brosch *et al.* may describe sequencing the termini of some BAC clones, the sequencing is for the purpose of determining the relative position of clones to each other and for analyzing possible repetitive sequences in the termini. *See*, Brosch *et*

al., page 2224, last paragraph in first column through first full paragraph in left column of page 2226. Significantly, Brosch *et al.* does not teach or suggest identifying corresponding sequences in a separate reference genome nor does the reference teach or suggest determining any relationship between the members of pairs of termini sequences in a reference genome as required in steps (iii) and (iv).

Brosch *et al.* does not teach or suggest obtaining the terminal sequences of clones and using that information in *any* way to compare genomes. In obviousness rejections based on Brosch *et al.* (discussed in further detail below), the Examiner points to the reference's discussion of using BACs to identify characteristics for identification of genomic differences. *See*, Office Action, page 4 citing Brosch *et al.*, page 2228, second paragraph. The paragraph specifically cited by the Examiner describes a method of digesting genomic clones and probing the restricted clones with labeled total DNA from another bacterial species. *See, e.g.*, third sentence of the second paragraph of page 2228 of Brosch *et al.* This method appears to be the only method of genomic comparison described in any way in the reference. This method does not involve sequencing termini of clones, identifying corresponding sequences in a reference genome or determining the relationship between the members of each pair of termini as recited in the claims. Accordingly, Brosch *et al.* cannot anticipate the present claims.

Applicants further note that claim 3 is directed to the use of a human genome. Brosch *et al.* does not teach or suggest use of *anything* other than use of BAC clones from *M. tuberculosis*. Therefore, Brosch *et al.* cannot anticipate claim 3.

4. Rejection under 35 U.S.C. § 103

A. Rejection over Brosch et al. over Alshtul et al.

Claim 1 was rejected under 35 U.S.C. § 103 as allegedly obvious over Brosch *et al.* in view of Alshtul *et al.* The Examiner asserted that Brosch *et al.* teaches "end sequencing profiling of a library of clones" and Alshtul *et al.* teaches computational methods of comparing sequences. Without any explanation or reference to a motivation in the art, the Examiner argues that "one skilled in the art would obviously be motivated

to determine if [the terminal sequences] have any physiological relevance." Applicants respectfully traverse the rejection.

The Examiner has not set forth a *prima facie* obviousness rejection because the cited references separately or together do not set forth all of the elements of the claims. The Examiner has not pointed to any motivation to determine the relationship between pairs of sequences from the termini of clones as recited in step (iv) and the subsequence "wherein" clause in claim 1. Without a description of each and every element in the cited art, the claims cannot be obvious.

As discussed above, the primary reference does not teach or suggest sequencing the termini of clones derived from the genome of an individual with a disease associated with chromosomal rearrangements and then identifying corresponding sequences corresponding to the end termini in a reference genome and then determining the relationship of the pairs of termini in the reference genome. As discussed above, at most the primary reference describes hybridizing total genomic DNA from one bacterial species to restriction digested clones from the genome of another bacterial species. The reference does not teach or suggest *any* use of terminal sequences in genomic comparisons, let alone suggest the claimed methods.

The only reason termini sequencing of clones is discussed in Brosch *et al.* is with regard to analysis of the sequence within the *same* genome (i.e., *M. tuberculosis*) to establish a BAC map (*see, e.g.*, the first full paragraph on page 224 of Brosch *et al.*) and to determine the status of possible repetitive ends (*see, e.g.*, the last paragraph on page 224 of Brosch *et al.*). Brosch *et al.* does not describe any use for terminal sequences in genomic comparisons, i.e., the reference does not teach or suggest identifying corresponding sequences in a reference genome or determining the relationship between the members of each pair of termini to determine chromosomal rearrangements.

Alshtul *et al.* does not correct these defects. The Examiner only states that those of skill in the art would be motivated to determine any "physiological relevance" of any sequence and therefore would turn to Alshtul *et al.*. The Examiner apparently argues that those of skill in the art would be motivated to use a BLAST algorithm to determine

whether end sequences of clones encoded proteins related to those in a database. This is **not** a motivation to determine the relationship between pairs of sequences from the termini of clones. At most the motivation cited by the Examiner is to investigate individual end sequences, not determine the relationship between pairs of sequences from ends of a clone as recited in steps ii-iv of the claims.

Moreover, Alshtul *et al.* does not address obtaining pairs of clone end sequences or determining the relationship *between* the members of the pair. Accordingly, Applicants request withdrawal of the rejection.

B. Rejection over Brosch et al.

The Examiner rejected claims 1-23 as obvious in view of Brosch *et al.* The Examiner argued that the differences between the cited reference and the claims were minor and were related to density of clones, permutations of test/reference genomes, etc. Applicants traverse the rejection.

As discussed above, Brosch *et al.* does not teach or suggest the claimed methods. Brosch *et al.* does not describe determining the relationship between pairs of termini sequences from clones from a test genome and corresponding sequences in a reference genome. Moreover, the Examiner does not point to any motivation to do so. To the extent Brosch *et al.* describes any sort of genomic comparisons, the comparisons involve hybridization of total DNA to restriction enzyme cleaved clones, **not** end sequencing. *See*, Brosch *et al.*, page 2226. The method described in Brosch *et al.* works in a completely different way than the claimed method. Thus, the differences between the method of Brosch *et al.* and the claims are *major*, not minor as suggested by the Examiner. Accordingly, Applicants request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A method for comparing a test genome to a reference genome, said method comprising:

(i) providing a plurality of clones of known size that substantially cover at least a portion of said test genome;

(ii) obtaining sequence information from the termini of each of said plurality of clones, thereby obtaining a pair of terminal sequences;

(iii) identifying a pair of sequences within said reference genome that corresponds to each of said pairs of terminal sequences; and

(iv) determining the relationship between the members of each pair of corresponding sequences within said reference genome;

wherein a difference in the observed relationship between the members of any of said pairs of corresponding sequences within said reference genome and the expected relationship based upon said known size of said plurality of clones indicates the presence of a rearrangement in said test genome compared to said reference genome and wherein said test genome is obtained from an individual with a disease associated with chromosomal rearrangements.